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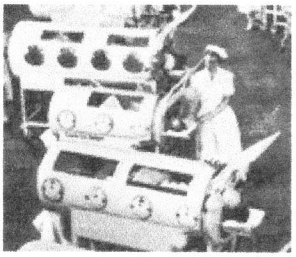

Warts on the Poliosaur Bones: The Successes and Failures of Poliomyelitis Vaccines in the US

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Abstract: Polio is almost gone but certainly not forgotten. Even though wild-type poliovirus has been eradicated from the Western Hemisphere, cases of vaccine-associated paralytic poliomyelitis still occur in the US and other developed countries. New guidelines that recommend the use of enhanced inactivated polio vaccine should reduce the number of cases.

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The epidemiology of an infectious disease can change dramatically over time. Paralytic poliomyelitis, a scourge of the first half of the 20th century, has gone the way of smallpox, at least in the US, a dinosaur to be read about but no longer found in real time (in the absence of Michael Crichton and Stephen Spielberg).

Unlike many others of my generation, my family and I were fortunate not to suffer from paralytic polio. However, polio has been intertwined with my life. Grandma Ada had my mom, as a child, wear garlic and camphor around her neck to ward off the disease. The vile odors kept her thin. When I was in elementary school in Brooklyn, New York, my class was part of a Salk polio vaccine trial. Years later, during my medical student years, I lived on the grounds of Kings County Hospital, Brooklyn, in a building that was the original Kingston Avenue Hospital where, decades before, hundreds of patients with paralytic polio had been cared for and characterized.[1] Finally in 1979, I became one of the few US-born and -trained physicians of my generation to assist in the care of Americans with wild-type virus poliomyelitis. These patients, who were from a nonimmunized religious group, were hospitalized at the University of Iowa Hospital.[2]

The post-polio syndrome. A fair amount of what is currently written about poliomyelitis revolves around the post-polio syndrome (PPS), which is the subject of a comprehensive review in this issue of INFECTIONS *in* MEDICINE. Developing 10 to 30 years after paralytic polio, PPS is a potential hazard for the estimated 640,000 surviving Americans who had paralytic polio in the 1940s and 1950s.[3] Although PPS was discussed in the medical literature of the 19th and early 20th centuries, a letter to the editor of the *Rehabilitation Gazette.* in 1979[4] from a polio survivor with this syndrome brought PPS into the forefront with a flood of responses. This outflow of recognition led to the First International Post-polio Symposium held in Chicago in 1981. For the young physician, however, learning about paralytic polio from PPS is not unlike studying dinosaurs from fossilized bones.

"Infantile paralysis." Unlike the myriad years during which dinosaurs dominated the Earth, the "poliosaur" ruled as a carnivore of humans for just a few decades. Undergoing a transition in this century from a rare endemic disease of early life ("infantile paralysis") to one with severe epidemic potential, polio became a major health hazard in the US. The explosion of polio was a price for progress, brought about by improved sanitation, hygiene, and living conditions that increased opportunities for infection in older children who had a higher risk for paralysis.[5] During this period, hospitals full of Drinker respirators, also known as "iron lungs" (Fig. 1), were common.

Figure 1. (click here to zoom image) Drinker respirators at work during polio epidemic. Reprinted from JAMA (1986; 255:1476-1480), Copyright © 1986, American Medical Association.[43]

In the mid-1950s, polio began the slide down the road to extinction--a road bearing the names Salk and Sabin. The poliovirus vaccines developed by these investigators and their colleagues, as well as the history of polio, have a significant presence in the medical literature.

Early vaccines. Approximately 3 decades after the 1909 transmission of polio to primates using a filtrate of CNS tissue inoculated intracerebrally, the first human field studies of both "attenuated" and formalin-treated polio-infected CNS tissue vaccines were undertaken. As noted by Robbins,[6] the trials were poorly conceived, with no adequate tests for safety and efficacy nor concern regarding the risk to

humans of the parenteral administration of myelinated CNS tissue. Some cases of paralytic disease resulted, and the trials were discontinued without any clear success.[7,8] Attempts were also made to prevent polio by chemical treatment of the nasal mucosa using picric acid, alum, and zinc sulfate to block viral invasion, but this methodology was also abandoned.[6]

A vaccine against poliomyelitis became a viable possibility following successful tissue-culture cultivation of poliovirus by Enders, Weller, and Robbins in 1949[9]; the recognition that there were only 3 antigenically distinct viral strains[10]; and the finding that human immune serum globulin administration prevented paralytic disease.[11] Work began in earnest on both inactivated and live attenuated polio vaccines.

IPV. The efficacy of trivalent, Salk, formalin-inactivated polio vaccine (IPV) was clearly demonstrated in a 1954 US field trial conducted by Thomas Francis and colleagues.[12] This large study involved more than 750,000 children in a placebo-controlled trial and an additional 1,100,000 in an observed open investigation. Protective efficacy of the vaccine was more than 90% for types 2 and 3 but only 60% to 70% for type 1. Replacement of the thimerosal preservative corrected the lower efficacy of type 1 vaccine that resulted from decreased immunogenicity caused by thimerosal.[6] Licensure of the vaccine was granted to 6 different manufacturers in mid-1955.

Soon after widespread use of IPV, reports of paralytic disease in some vaccine recipients surfaced; these individuals experienced paresis of the inoculated limb and an onset of disease compatible with pathogenic virus contaminating the vaccine.[13,14] Investigation found that almost every case occurred in children, or the contacts of children, who had received certain lots from 1 manufacturer, Cutter, which fortunately had marketed the smallest amount of vaccine. New safety requirements and a filtration step to remove agglutinated virus less sensitive to formalin inactivation quickly resolved this problem. However, almost 200 cases of paralytic disease had resulted from the "Cutter incident."

Because of prevailing fears of paralytic polio at the time, the episode did not reduce vaccine acceptance. If such an episode occurred in the present day, it is likely that significant decrease in compliance with many vaccines would occur. After the changes made in IPV manufacture, no further overt problems with this vaccine occurred.

SV40. Adventitious latent viruses contaminating polio vaccines from the use of primary cell cultures, however, have been a concern. In 1960, simian virus 40 (SV40) was found to cause inapparent infection of rhesus monkey kidney cells that produced vacuolation in other cell lines. In retrospect, SV40 had contaminated some lots of inactivated and live polio vaccines produced in rhesus monkey kidney cells. Formaldehyde inactivation kinetics of SV40 were such that the virus could survive an exposure quite adequate to kill poliovirus.[15] Some individuals receiving IPV or oral polio vaccine developed antibodies to SV40[16] and, in fact, SV40 was isolated from the stool of some persons receiving oral polio vaccine (OPV).[17] The concern about human exposure to SV40 centered around malignant potential in animals and transformation of cells in tissue culture. Long-term investigations (almost 20 years) of populations that had likely received SV40-contaminated vaccine, however, have not shown any increase in malignancies or overall mortality.[18,19]

More recent studies have found SV40 T-antigen DNA sequences in human CNS,[20] bone,[21] and pleural mesotheliomas.[22] Additionally, pleural mesotheliomas have been reported to be induced in hamsters inoculated with SV40.[23] In one study of 83 CNS tumors of various histologic types,[20] 32 were found to have SV40 sequences. Interestingly, 61% of the patients with SV40 sequences were of an age that excluded exposure to SV40-contaminated polio vaccine. The investigators suggested that horizontal SV40 transmission could explain these findings, since peripheral blood cells and seminal fluid also contained these sequences. No clear direct association has been proven, however, between SV40-contaminated vaccine and cancer in humans. In the same vein, the hypothesis that the AIDS epidemic originated from an HIV or SIV agent possibly contaminating polio vaccine has been examined

using sensitive detection methods, but no evidence of HIV/SIV was found.[24]

In 1961, 6 years after the introduction of IPV into the US, the incidence of paralytic polio had decreased by more than 90%, as compared with the incidence during the prevaccine period (Fig. 2). The drop in the number of polio cases occurred despite only 54% of the population--primarily the younger age groups--having received at least 3 doses or more of IPV.[25] Age-specific attack rates in nonvaccinated individuals also decreased in all groups during this period (Fig. 3), showing community (herd) protection.[26]

Figure 2. (click here to zoom image) Annual number of cases of paralytic poliomyelitis in US, 1951-1978. Adapted from Rev Infect Dis (1980; 2:228-242), Copyright © 1980, University of Chicago Press.[44]

Figure 3. (click here to zoom image) Age-related attack rates of paralytic poliomyelitis in US, postvaccine (1957-1960) vs prevaccine (1951-1954). Adapted from Rev Infect Dis (1980; 2:243-257) Copyright © 1980, University of Chicago Press.[26]

OPV. A number of research groups were developing live attenuated OPVs during this time period. The OPV candidate needed to replicate enterically in order to induce neutralizing antibody, not infect the CNS, and be genetically stable enough so that passage in humans did not cause reversion to increased neurovirulence. Because of the lack of a precise in vitro marker for virulence, a monkey neurovirulence (MNV) assay was adopted by regulatory agencies to assess neurovirulence of the vaccine viruses. MNV is assessed by the direct CNS inoculation of the vaccine virus into the simian thalamus and spinal cord. This route was selected for a higher sensitivity, not for mimicking human OPV exposure. Interestingly, the rhesus monkey used is relatively resistant to the oral route of infection for poliovirus.

Large field trials of OPV were conducted primarily outside the US. By 1960, more than 100,000,000 individuals in Russia and other eastern European countries had received the product. Licensure in the US was granted based on the evaluation of these studies,[6] and Sabin OPV became the polio vaccine of choice in the US. This occurred because it was believed that OPV, not IPV, could have a pronounced effect on the spread of wild-type polio in the community; that OPV would produce more permanent and complete immunization of the population than IPV; and that OPV could be given without a risk of paralysis.[27]

In retrospect, it appears that none of these beliefs were true.[28] Not only could reasonable herd immunity be produced using IPV, but also elimination of wild poliovirus strains was accomplished in countries that continued to use only IPV.[29] Researchers have also questioned whether OPV induces an intestinal immunity that is as effective and long-lasting as had been generally believed. Salk[26] reviewed this issue referring to studies that have found, given a significant enough challenge, that either IPV or OPV immunity can be overcome to produce intestinal reinfection. Additionally, in the 1979 multicountry outbreak of wild-type 1 virus, immunity to wild-type poliovirus appeared just as strong in Dutch IPV-vaccinated individuals as in American OPV recipients.

If OPV did not cause paralytic disease, then these other comparison points would be relatively moot, as OPV is more convenient to use and less expensive than IPV. However, recognition occurred quite early in the OPV era that paralytic disease could be related to this biologic. In fact, the US Surgeon General's Oral Poliomyelitis Vaccine Advisory Committee--because of the recognition of cases of paralytic poliomyelitis, particularly with the type-3 vaccine virus--recommended the consideration of restricting type-3 OPV to only high-risk (for wild-type poliovirus) children and adults.[30] Previously, a US Surgeon General statement had considered OPV types 1 and 2 satisfactory for use but had been concerned about the tendency of type 3 to change its MNV after human enteric passage.[31] In evaluating the stability of

the attenuated vaccine, it had become clear that when attenuated type-3 poliovirus was given to a human, the virus found in the stool that could be (and often was) acquired by a close contact was significantly more neurovirulent. In fact, the excreted type-3 virus often could not pass US federal regulations regarding the amount of MNV allowed in the vaccine virus,[5] which required that the vaccine monopool lots be no more neurovirulent than the National Institutes of Health (NIH)-reference type-1 strain.[32]

A number of lawsuits regarding the development of vaccine-associated paralytic poliomyelitis (VAPP) have argued that the illness was related to the failure of the Division of Biologic Standards of the NIH (now the Bureau of Biologics of the FDA) to follow the regulations for the release of type-3 OPV. It was found that over the years, the regulatory agency had violated the law related to the neurovirulence of the type-3 vaccine strain.[33] It is reasonable for some small, but finite, risk with the use of OPV to exist as a trade-off for the overall public good. But violation of federal law written to minimize such neurovirulence is not reasonable because increased OPV neurovirulence in monkeys should denote a corresponding increase in human neurovirulence.

eIPV. In 1988, an enhanced potency IPV (eIPV) began to be distributed in the US. The enhanced immunogenicity was primarily a result of a microcarrier technique that produced substantially higher amounts of viral antigen at lower cost. The enhanced vaccine allowed adequate immunization with fewer doses.[34,35] Notably, human diploid cells can be used as a substrate in this system instead of monkey kidney cells, thus obviating concerns about latent primate viruses.

New guidelines. In mid-1996, the US Public Health Service Advisory Committee on Immunization Practices (ACIP) made the most significant change in the US poliovirus immunization schedule since the introduction of OPV in 1961. The new guidelines, published in 1997, formally recommended initial immunization using eIPV for the first 2 doses, followed by OPV for the second 2 doses of the primary schedule.[36] The ACIP would also accept 4 doses of OPV (as before) or, alternatively, 4 doses of eIPV as the primary regimen. The American Academy of Pediatrics (AAP) recommended that the initial 2 doses be eIPV, followed by either eIPV or OPV. The American Academy of Family Physicians (AAFP) has chosen to recommend parent-provider choice among sequential (eIPV/OPV), all-eIPV, or all-OPV schedules.

The rationale for this change is similar to that for the discontinuation of routine smallpox vaccination in 1978.[37] Since smallpox had been essentially eradicated, the complications of vaccination in the US infinitely outweighed any protective benefits. As of this writing, there has been no documented case of wild-type paralytic polio in the US since 1979, and only about 8 to 10 cases of VAPP occur each year.[38] These cases occur both in vaccinees, some of whom are immunocompromised, and in contacts, such as the susceptible parent of the vaccinee.[38] Many clinicians, myself included, have routinely recommended eIPV to the parents of neonates prior to the use of OPV in the children, if the immunization history of the parents was unclear.

As reported by *The New York Times*[39] a number of citizen groups were concerned about the change in childhood immunization recommendations because of the increased number of injections per visit and the increased cost of the vaccine, both of which could reduce compliance. Certainly, unless or until a combination vaccine containing eIPV is marketed, the change dictates another inoculation and probable compliance problems in the delivery of an increased number of inoculations, particularly in the public sector. A new combination *Haemophilus influenzae*.type b/hepatitis B virus (Hib/HepB) vaccine[40] should assist in alleviating this. New vaccines continue to appear--increasing the number of inoculations needed to facilitate their use and, in turn, increasing the delivery burdens on the public and health care providers, at least until more combination products are available.

The new polio vaccine strategy will increase cost because eIPV is more expensive than OPV; however, despite the increased cost, it is well worth the effort to further minimize and eventually eliminate VAPP. Not all support the change in recommendations or this view, however.[41]

Conclusions. We must continue to be diligent in obtaining universal and safe immunization of our children. A pediatrician's habit of using OPV and/or a concern about an increased number of inoculations should not delay the implementation or minimize the importance of the new vaccination recommendations. The lay press continues to produce exposés on the vaccine industry, many of which are less than complimentary.[42] A program to improve the process of ensuring vaccine compliance using the principles of continual quality improvement along with appropriate maintenance of vaccines during shipping and storage can and will adequately immunize our children.

The new ACIP guidelines provide the opportunity for eliminating VAPP in the US. It is not the case, however, that OPV has had a fallible safety record. OPV for the population as a whole is safe and has helped prevent many millions of cases of paralytic polio. When the analysis switches from millions of OPV vaccinees (the Public Health) to the approximately 10 reported cases per year of VAPP (the public health), however, *primum non nocerum.*becomes the watchword.

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